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Papaverine:
The Ideal Coronary Vasodilator for Investigating Coronary Flow Reserve? A Study of Timing, Magnitude, Reproducibility, and Safety of the Coronary Hyperemic Response After Intracoronary Papaverine

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A potent, short-acting vasodilator that induces a maximal hyperemic response of the coronary vascular bed is needed to determine coronary flow reserve. In 12 patients, we measured coronary sinus blood flow by thermodilution over a period of 2 min during which a bolus of 10 mg papaverine was given into the left main coronary artery. This was repeated after 5 min to assess the reproducibility of the changes. The maximal hyperemic response lasted from 24 until 37 sec after papaverine administration. There was no significant difference between the two consecutive hyperemic responses (Student's t-test for paired observations). The mean difference between first and second hyperemic responses at 30 sec was 7.0% (SD ± 6.2%).

In conclusion, 10 mg of intracoronary papaverine is a short-lasting and reproducible means of inducing a maximal hyperemic response in the coronary vascular bed and therefore appears to be the ideal agent for investigating coronary flow reserve.

Key words: coronary flow reserve, coronary artery disease

INTRODUCTION

The concept of coronary flow reserve is essential in understanding the physiological significance of obstructive coronary artery disease [1,2]. The recent development of methods such as digital subtraction cine angiography or subselective coronary artery blood flow velocity measurements using a Doppler catheter have made the assessment of regional coronary flow possible during routine cardiac catheterization [3,4]. Coronary reactive hyperemia defined as the ratio of maximal coronary blood flow to resting flow can be used as a measurement of coronary flow reserve. In order to detect a limitation in coronary flow reserve due to an obstruction in a major epicardial coronary artery, measurements should be obtained when distal coronary resistance has been minimized by dilating this arteriolar bed pharmacologically [1]. Since the advent of interventional catheterization, multiple assessment of coronary flow reserve is mandatory, for instance to evaluate the effect of an intervention or to assess coronary flow reserve in different myocardial regions [3]. Long-acting vasodilators, such as dipyridamol, not only make multiple assessments of the hyperemic response impossible but may also give undesirable side effects such as a long-lasting endo-epicardial redistribution of coronary blood flow with a concomitant increase in oxygen consumption [5], thereby inducing ischemia and angina pectoris.

Therefore, a potent, short-acting vasodilator that will induce a maximal hyperemic response is needed to facilitate an accurate and reproducible means of determinating coronary flow reserve. When digital subtraction cineangiography is used to measure coronary flow reserve, angiograms during maximal hyperemia must be compared with baseline angiograms. Timing of the peak hyperemic effect is then of crucial importance. We studied reproducibility, timing, and duration of the coronary hyperemic response after intracoronary papaverine by measuring coronary sinus blood flow with thermodilution.

PATIENTS AND METHODS

Twelve patients who underwent cardiac catheterization and coronary angiography for clinical indications were studied after informed consent was obtained. The patients were studied without sedation, following overnight fasting. All medication was withheld on the day of the

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catheterization. A thermodilution catheter (Webster laboratories) was introduced after percutaneous puncture of the femoral vein or after cutdown of a right antecubital vein and positioned in the coronary sinus. Catheter position was verified by contrast injection. Coronary sinus blood flow was measured according to the thermodilution technique by infusing saline 50 ml/min with a Medrad mark IV infusion pump. The temperature of the coronary sinus blood was measured at 25 sec^{-1} from which flow was calculated (ml/min) and averaged for 5-sec intervals (see Fig 1a, 1b). In each patient, a stable position of the catheter was assured by fluoroscopy and a stable baseline measurement was recorded. Thereafter, the coronary catheter was inserted after percutaneous puncture of the femoral artery or after cutdown of the brachial artery. The tip was positioned into the ostium of the left main coronary artery under fluoroscopy. Coronary sinus blood flow was measured continuously over 2 min during which a bolus of 10 mg papaverine was given into the left main coronary artery to record the timing and magnitude of the coronary hyperemic response. This was repeated after 5 min to assess reproducibility of the changes. Reproducibility was assessed by comparing for first and second injections of papaverine the ratio of coronary sinus blood flow 30 sec after intracoronary papaverine to baseline flow.

The spontaneous variations of all 5-sec intervals of the baseline flows were used to calculate the standard deviation of the mean baseline flow expressed in percentage. This standard deviation was used to define the duration of the plateau phase of the maximal hyperemic response. Systemic arterial pressure and heart rate were recorded continuously. Thereafter, the diagnostic study was completed.

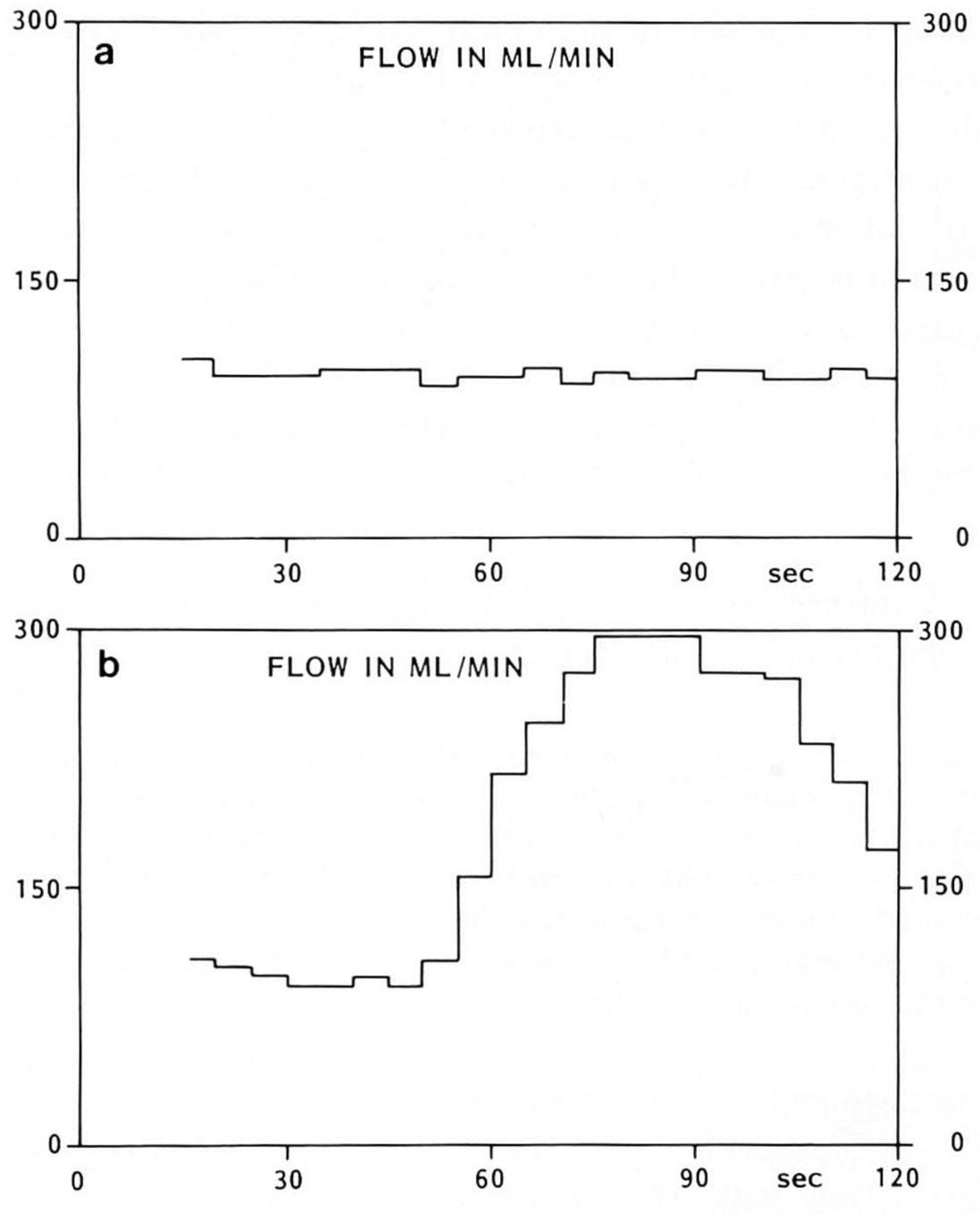

Fig. 1. Coronary sinus blood flow measurement with thermodilution. a. Stable baseline recording. b. Recording during a 10-mg bolus injection of papaverine into the left main coronary artery.

RESULTS

Patient Characteristics

The patient characteristics are shown in Table I. The mean age of the patients was 57.4 years (range 48–67); ten were male, two female. Four patients had no angiographic significant coronary artery disease (>50% diameter stenosis), four patients had one-vessel disease, two patients had two-vessel disease, and two patients had three-vessel disease. The mean left ventricular ejection fraction was 67% (range 44–76%).

TABLE I. Patient Characteristics*

Patient No.	Age	Sex	CAG	LVEF (%)
1	55	M	0	44
2	64	M	0	59
3	60	M	1	64
4	57	F	0	66
5	63	M	2	65
6	67	M	2	50
7	59	M	1	67
8	62	F	1	76
9	48	M	3	66
10	61	M	3	65
11	61	M	1	70
12	52	M	0	66

*CAG, coronary arteriogram, number of vessels with lesions of >50%; LVEF, left ventricular ejection fraction.

Timing of the Coronary Hyperemic Response

The average plateau phase of the maximal hyperemic response was reached after 24 sec and lasted up to 37 sec after the intracoronary injection of papaverine (Fig. 2). The peak effect of individual intracoronary injections was reached after a mean time of 31.3 sec, (standard deviation ± 3.4 sec). Peak hyperemia following each individual papaverine injection (n = 24) was within the defined plateau phase of the maximal hyperemic response.

Magnitude of the Coronary Hyperemic Response

The mean baseline coronary sinus blood flow was 105.7 (range 71–175) ml/min before the first papaverine

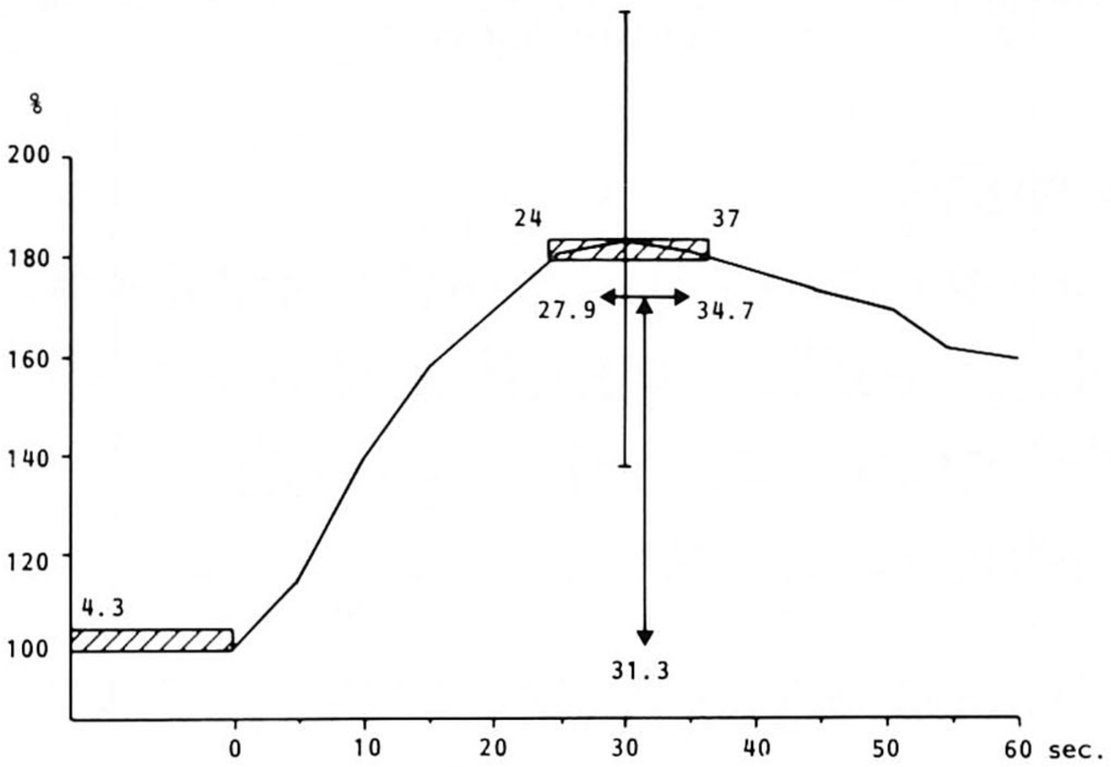

Fig. 2. Timing of the average coronary hyperemic response of all 24 papaverine injections. The shaded area is 1 SD calculated from the spontaneous variations in the baseline recordings. The plateau phase of the hyperemic response lasted from 24 until 37 sec after the intracoronary injection of papaverine. The peak effect of the injections was reached after a mean time of 31.3 sec (standard deviation ± 3.4 sec).

injection and rose to a mean peak value of 194.4 (range 130–325) ml/min. The mean baseline coronary sinus blood flow was 109.6 (range 69–180) ml/min immediately before the second papaverine injection and rose to a mean peak value of 196.1 (range 97–398) ml/min.

In Figure 3a, the percentage increase in coronary sinus blood flow (mean and standard deviation) is shown after all papaverine injections (n = 24). Coronary vascular resistance was calculated as systemic arterial pressure divided by coronary sinus blood flow and is shown in Figure 3d.

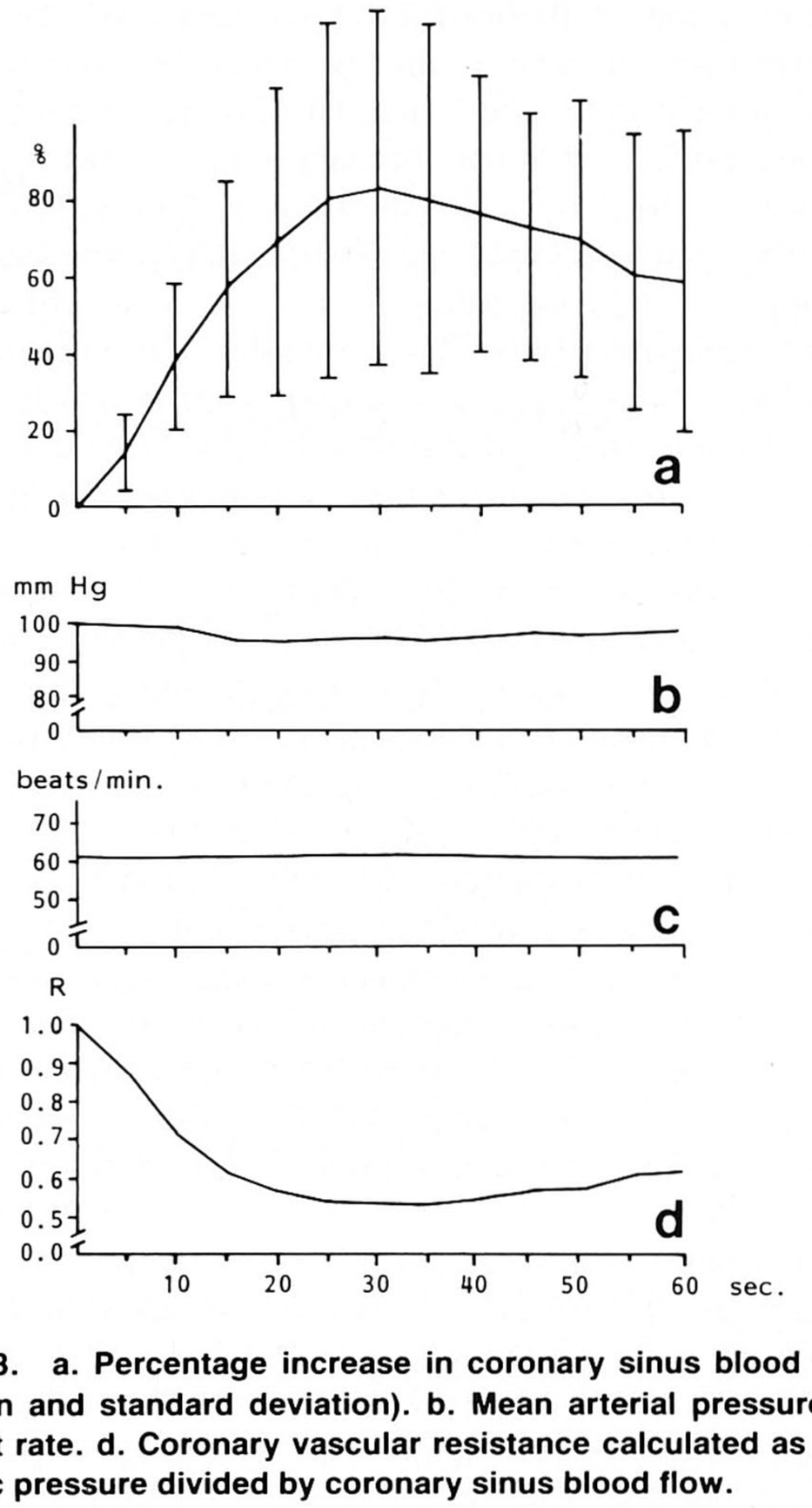

Fig. 3. a. Percentage increase in coronary sinus blood flow (mean and standard deviation). b. Mean arterial pressure. c. Heart rate. d. Coronary vascular resistance calculated as systemic pressure divided by coronary sinus blood flow.

Reproducibility of the Coronary Hyperemic Response

In Figure 4, the percentage increase in coronary sinus blood flow after the first papaverine injection is plotted versus the percentage increase in coronary sinus blood flow after the second papaverine injection; linear regression showed an r-value of 0.92. There was no significant difference (Student's t-test for paired observations) in magnitude or timing of the hyperemic response between first and second injections or in baseline coronary sinus blood flows. The responses of individual patients to first and second injections are shown in Figure 5. The difference between the first and the second hyperemic response, 30 sec after papaverine injection, was calculated as a percentage of the coronary sinus blood flow (see Table II). The average difference was 7.0% with a SD of 6.2%.

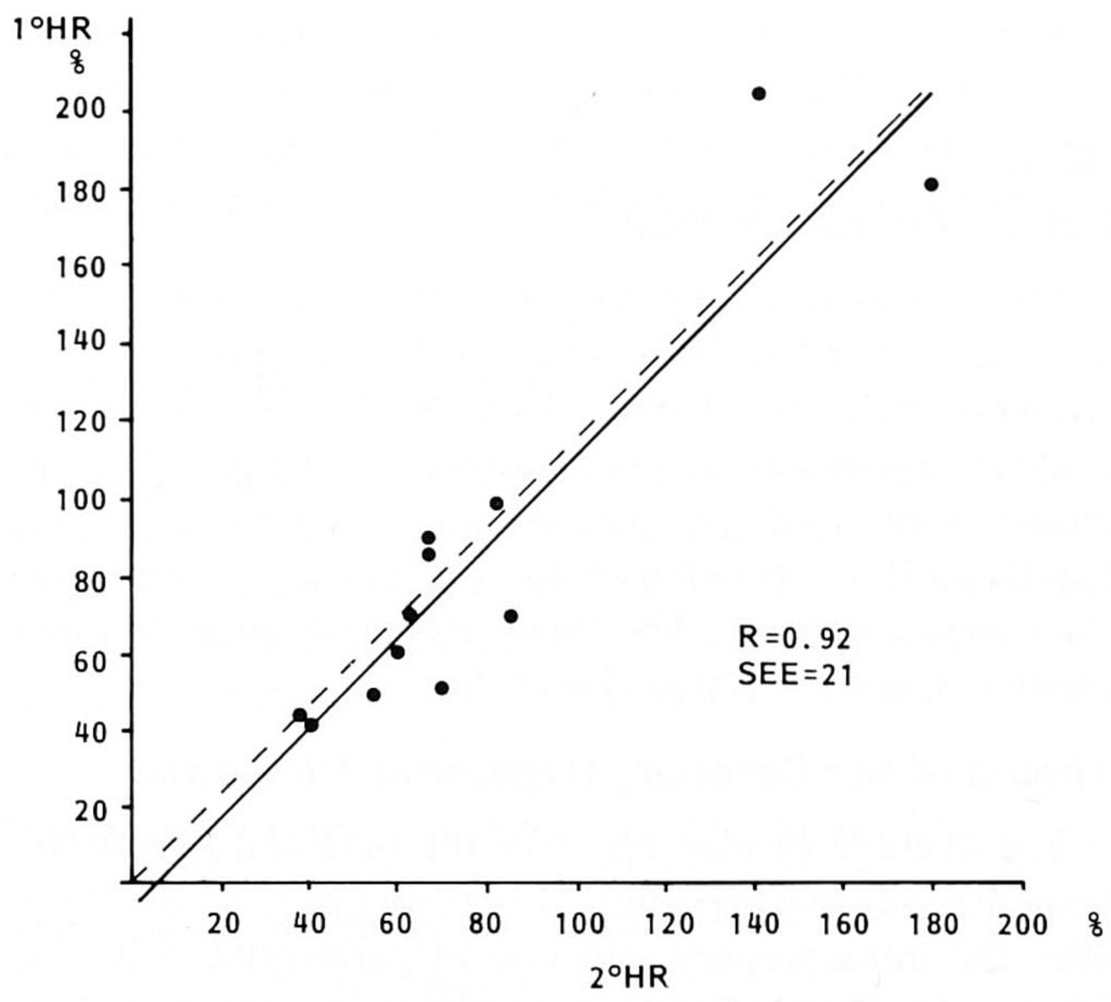

Fig. 4. Reproducibility of the coronary hyperemic response after intracoronary papaverine. 1° HR, first hyperemic response; 2° HR, second hyperemic response.

Safety

There was no significant effect of the intracoronary given papaverine on either systemic arterial pressure or

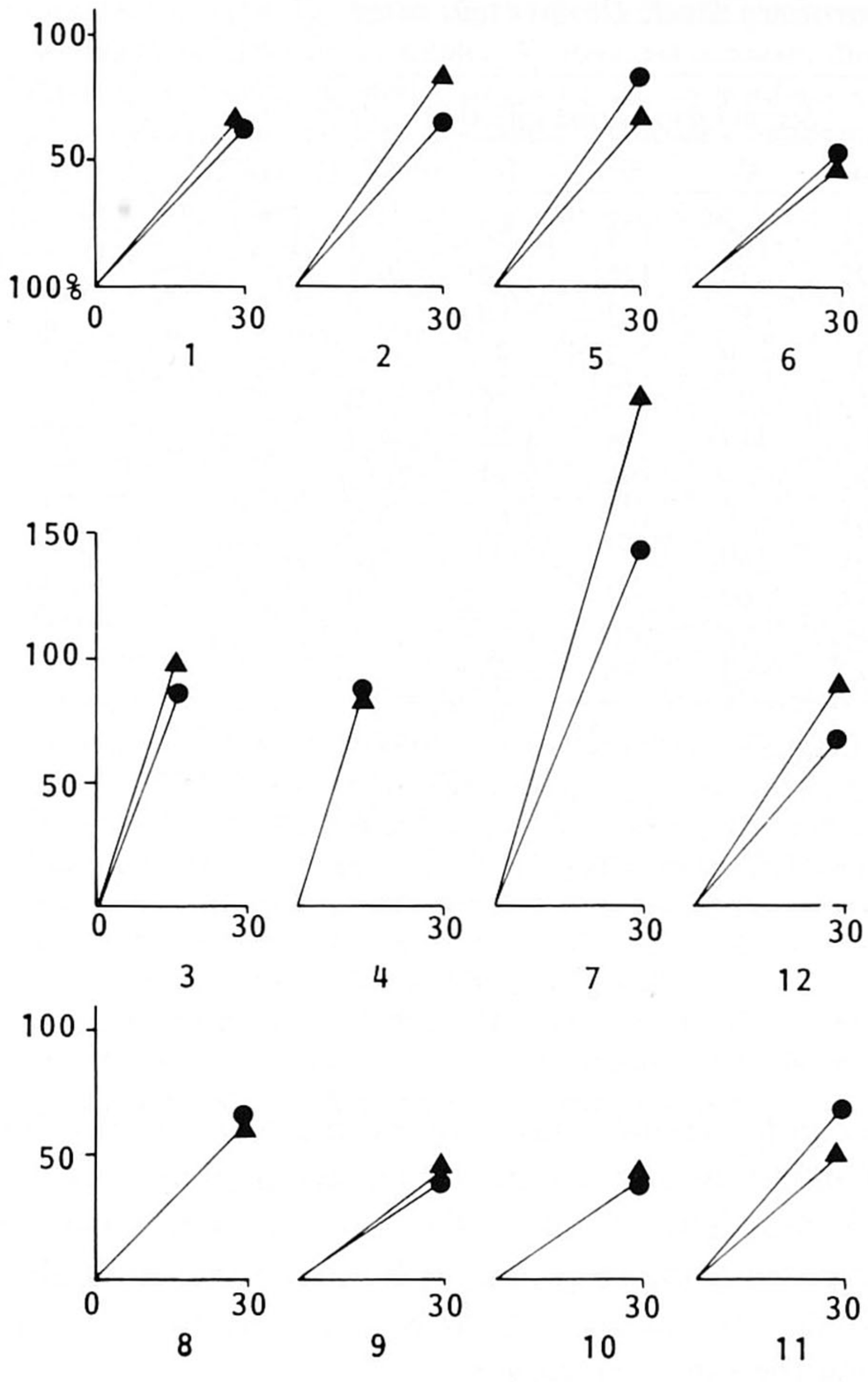

Fig. 5. Responses of individual patients to first (▲) and second (●) injections of papaverine. Numbers 1–12 correspond to patients 1–12 in Table I and II. The ordinates present percentage increase of coronary sinus blood flow. On the abscissas: 0, before papaverine injection; 30, 30 sec after papaverine injection.

heart rate (Fig. 3b,c). No patient reported angina pectoris despite striking changes in the repolarization phase of the surface electrocardiogram [6], and no complications occurred during the procedure.

DISCUSSION

Visual interpretation of the coronary angiogram is a poor means of predicting the physiological importance of obstructive coronary artery disease [7]. Computer-based quantitative analysis of the coronary angiogram has solved, insofar as currently possible, the problems of high interobserver and intraobserver variability and makes calculation possible of hydrodynamic parameters of the coronary artery lesion that are correlated with translesional pressure gradient and thallium perfusion scintigraphy [8–11]. Even so, the relation between the quantitatively analyzed coronary artery lesion and its hydrodynamic repercussion is not fully understood and methods that assess the limitation in coronary flow reserve due to an obstructive lesion are therefore needed. Various ways to study coronary flow reserve have been described [1–4,12]. Induction of a hyperemic response is an essential part of all these methods. The recent description of a digital angiographic technique to measure relative coronary blood flow makes assessment of coronary flow reserve during routine cardiac catheterization possible [4]. A safe, reproducible way of inducing a maximal hyperemic response is therefore all the more imperative [2].

Assessment of Coronary Hyperemic Response With Thermodilution Measurements of Coronary Sinus Blood Flow.

A wide range of values for the coronary flow reserve of normal coronary arteries is reported, depending on the vasodilator used and the measuring technique [3,12–16]. The carefully validated studies with a Doppler catheter suggest that the maximal coronary blood flow of a normal coronary artery is 4 to 6 times resting flow [3]. The thermodilution measurements of coronary sinus blood flow have shown the highest flow increment reported in the literature, namely hyperemic flow 3 times resting flow, which was indeed observed in some of our patients [17]. With thermodilution, Foult et al studied the coronary hyperemic response following a coronary angiogram with a hyperosmolar ionic contrast medium and measured a ratio of maximal flow to resting flow of only 2, for patients with normal coronary arteries. However, there was a significant relation between the coronary hyperemic response and the extent of the coronary artery disease [15]. Our results (compare Tables I and II) show a similar trend. Since we were not specifically interested in the absolute changes in flow but especially in timing and reproducibility of the flow changes, we felt that thermodilution, which gives continuous recordings and is easy to repeat, was in this particular instance an adequate technique of investigation. The frequency response of the measurement is sufficient to measure changes in flow that occur within 2 to 3 sec [1,18,19].

Vasodilator Agents

The most widely used vasodilator agents are dipyridamol and hyperosmolar ionic contrast media [1,3–5,7]. An intravenous infusion of dipyridamol in adequate dosage results in a maximal coronary vasodilation, but its use has several disadvantages [16].

First, its long-lasting effect makes repeated assessment of the hyperemic response of a coronary vascular bed or assessment of different coronary vascular beds during the same procedure impossible [3]. Second, the long-lasting endo-epicardial redistribution of coronary blood flow in conjunction with an increase in myocardial oxygen con-

TABLE II. Reproducibility of Changes in Coronary Sinus Blood Flow After Intracoronary Papaverine*

Patient No.	First papaverine injection				Second papaverine injection				
	Aol	A	B	C	Ao2	D	E	F	G[a]
1	90	102	173	1.70	92	106	174	1.64	3.5
2	103	71	132	1.86	105	75	126	1.68	9.7
3	91	91	181	1.99	85	83	153	1.84	7.5
4	106	78	219	2.81	107	79	223	2.82	0.3
5	83	94	159	1.69	79	95	177	1.86	10.0
6	82	117	174	1.49	83	119	184	1.55	4.0
7	89	110	335	3.05	90	164	398	2.43	20.3
8	106	90	144	1.60	104	115	185	1.61	0.6
9	105	175	252	1.44	101	180	251	1.39	3.5
10	96	99	140	1.41	98	69	97	1.41	0.0
11	82	86	130	1.51	82	76	130	1.71	13.2
12	110	155	294	1.90	106	154	259	1.68	11.6

*Aol, mean aortic pressure (mm Hg) during the first papaverine injection; A, baseline measurement (ml/min); B, measurement 30 sec after intracoronary papaverine; C, ratio of B/A; Ao2, mean aortic pressure during the second papaverine injection; D, second baseline measurement; E, measurement 30 sec after intracoronary papaverine; F, ratio of E/D; G, difference between C and F in percentage, calculated as (C − F)/C. Mean difference: 7.0% with a standard deviation of 6.2%.
[a]Mean 7.0%; SD ± 6.2%.

sumption [5] may induce ischemia that can only be terminated by the intravenous administration of aminophylline [16]. Hyperosmolar ionic contrast media do not produce maximal arteriolar vasodilation [2,6,13]. Bookstein and Higgins have shown in dogs that the coronary hyperemic response after a bolus injection into a coronary artery of adenosine-triphosphate or papaverine is of the same magnitude as after a 15-sec occlusion of the coronary artery [6]. Hodgson and Williams compared in human beings the coronary hyperemia induced by a hyperosmolar ionic contrast medium with papaverine and observed a twofold greater hyperemic response after papaverine [13]. The exact dosis of intracoronary papaverine needed to produce maximal coronary vasodilation has recently been established. Wilson and White compared the coronary hyperemic response after 4,8,12, and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 mg in most coronary arteries and after 12 mg in all coronary arteries. Papaverine at this dosage (8–12 mg) produced a response equal to intravenous infusion of dipyridamol in a dosage of 0.56 to 0.84 mg/kg. The coronary blood flow velocity after papaverine and dipyridamol was 4.8 times resting coronary blood flow velocity [14].

In conclusion, this study shows that reproducibility of the coronary hyperemic response after intracoronary papaverine is excellent. Timing of the peak effect is crucial if a digital angiographic technique is to be used because angiograms during maximal hyperemia have to be compared with baseline angiograms. We measured the time interval after intracoronary papaverine during which hyperemia is maximal, and showed the practical feasibility of making an angiogram during maximal arteriolar vasodilation. The effect of the intracoronary papaverine disappears completely within 5 min so that multiple assessments of coronary flow reserve can be undertaken during the same procedure.

CONCLUSIONS

Ten milligrams intracoronary papaverine is a safe and reproducible means of inducing a strong hyperemic response in the coronary circulation with a peak effect lasting from 24 until 37 sec and a duration of action less than 5 min, and therefore seems an ideal agent for investigating coronary flow reserve.

REFERENCES

1. Klocke FJ: Measurements of coronary blood flow and degree of stenosis: Current clinical implications and continuing uncertainties. J Am Coll Cardiol 1:31–41, 1983.
2. Hoffman JIE: Maximal coronary flow and the concept of coronary vascular reserve. Circulation 70:153–159, 1984.
3. Wilson RF, Laughlin DE, Ackell PH, Chilian WM, Holida MD, Hartley CJ, Armstrong ML, Marcus ML, White CW: Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 72:82–92, 1985.
4. Hodgson J, Le Grand V, Bates ER, Mancini GBJ, Aueron FM, O'Neill WW, Simon SB, Beauman GJ, Lefree MT, Vogel RA: Validation in dogs of a rapid digital angiographic technique to measure relative coronary blood flow during routine cardiac catheterization. Am J Cardiol 55:188–193, 1985.

5. Opherk D, Zebe H, Weihe E, Mall G, Dürr C, Gravert B, Mehmel HC, Schwarz F, Kübler W: Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. Circulation 63:817–825, 1981.
6. Bookstein JJ, Higgins CB: Comparative efficacy of coronary vasodilatory methods. Invest Radiol 12:121–127, 1977.
7. White CW, Wright CB, Doty DB, Hiratzka LF, Eastham CL, Harrison DG, Marcus ML: Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 310:819–824, 1984.
8. Serruys PW, Wijns W, Reiber JHC, de Feyter P, Brand M van der, Piscione F, Hugenholtz PG: Values and limitations of transstenotic pressure gradients measured during percutaneous coronary angioplasty. Herz 6:337–342, 1985.
9. Serruys PW, Reiber JHC, Wijns W, Brand M van den, Kooyman CJ, Katen HJ ten, Hugenholtz PG: Assessment of percutaneous transluminal coronary angioplasty by quantitative coronary angiography: Diameter versus densitometric area measurements. Am J Cardiol 54:482–488, 1984.
10. Reiber JHC, Serruys PW, Kooyman CJ, Wijns W, Slager CJ, Gerbrands JJ, Schuurbiers JCH, den Boer A, Hugenholtz PG: Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. Circulation 17:280–288, 1985.
11. Wijns W, Serruys PW, Reiber JHC, van den Brand M, Simoons ML, Kooyman CJ, Balakumaran K, Hugenholtz PG: Quantitative angiography of the left anterior descending coronary artery: Correlation with pressure gradient and results of exercise thallium scintigraphy. Circulation 71:273–279, 1985.
12. Goldman S, Henry R, Ovitt T, Friedman MJ, Rosenfeld A, Daly M: Regional myocardial perfusion at rest and during intracoronary papaverine in patients with coronary artery disease. Am Heart J 105:372–379, 1983.
13. Hodgson JM, Williams DO: Superiority of intracoronary papaverine to radiographic contrast for measuring coronary flow reserve in patients with ischemic heart disease. Circulation 72:(III)453, 1985.
14. Wilson RF, White CW: Intracoronary papaverine: An ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation 73:444–451, 1986.
15. Foult JM, Nitenberg A, Tovolaro O: Studies of contrast medium induced coronary reactive hyperemia: Implications for the evaluation of coronary reserve by digital angiography. Circulation 72:(III)261, 1985.
16. Marcus ML: Pharmacologic agents. In: "The Coronary Circulation in Health and Disease." McGraw-Hill, 1983, pp 417–452.
17. Berland J, Velu C, Cribier A, Letac B: Coronary reserve: A sex related difference in patients with angina and normal coronary angiography. Circulation 72:(III)387, 1985.
18. Ganz W, Tamura A, Marcus HS, Donoso R, Toshida S, Swan HJC: Measurements of coronary sinus blood flow by continuous thermodilution in man. Circulation 44:181–95, 1971.
19. Marcus ML: Methods of measuring coronary blood flow. In: "The coronary circulation in health and disease." McGraw-Hill, 1983, pp 25–64.